Remarks

Claims 1-37 are pending in the application. Claim 1-21 and 30-37 are withdrawn from consideration as directed to a non-elected invention. Claims 22-29 are presently under examination.

Regarding the Interview on January 22, 2004

Applicants thank the Examiner for taking the time to prepare for and meet with Applicants' representative on January 22, 2004, as well as for the helpful discussion of this application.

During the interview Applicants representative and the Examiner discussed the written description rejection and the separate enablement rejection under the first paragraph of section 112 of the Code. With regard to written description, the issue of whether the specification provides written description beyond the $Appl^D$ strain was discussed. Applicants' representative argued that the specification throughout, for example, at page 14, describes many additional strains that are useful for practicing the claimed methods, a fact that the Examiner agreed to take into consideration once submitted in writing. With regard to enablement, Applicants' representative and the Examiner discussed to issues. First, Applicants' representative argued that the Luo *et al.* reference cited by the Examiner supports a correlation in both structure and function between the Drosophila APPL protein product and its mammalian homolog APP. Second, Applicants' representative argued that the invention contemplates performing matings between organisms suitable for genetic analysis that have human disease gene homologs rather than the creation of transgenic organisms. Again, the Examiner indicated that the arguments in support of enablement will be given due consideration once submitted in writing.

Regarding the Rejections under 35 U.S.C. § 112, First Paragraph

Written Description

Applicants traverse the rejection of claims 22 to 29 under 35 U.S.C. § 112, first paragraph, as lacking written description of the claimed invention sufficient to show that the inventors were in possession of the invention at the time the application was filed.

Base claim 22 is directed to a method of identifying a therapeutic agent for treating Alzheimer's disease by performing matings between a first parent strain carrying a mutation in an Alzheimer's disease gene and a second parent strain containing a genetic variation, whereby test progeny are produced, where, in the absence of an agent, the parent strains produce test progeny having an altered phenotype relative to at least one sibling control; administering an agent to at least one strain selected from the group consisting of the first parent strain, the second parent strain and the test progeny; and assaying the test progeny for the altered phenotype, wherein a modification of the altered phenotype producing a phenotype with more similarity to a wild type phenotype than the altered phenotype has to the wild type phenotype indicates that the agent is a therapeutic agent.

In particular, the Examiner alleges that, at the time the above-identified application was filed, Applicants were not in possession of parental strains other than the Drosophila *Appl*^{D}. It is specifically asserted at page 5, first complete paragraph, that "the specification provided only *Appl*^{D}". Based on this premise, it is concluded that the possession of only *Appl*^{D} is not representative of the claimed genus (current Office Action, Paper No. 17, page 5, second complete paragraph). The Office cites *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997), to support the proposition that the genus of parental strains encompassed by Applicants' claims is not described in sufficient detail to allow the skilled person to conclude Applicants were in possession of the claimed invention.

As discussed during the interview and below, the Examiner's premise that the specification provides only *Appl*^{D} as a parental strain useful for practicing the claimed invention is respectfully submitted to be incorrect. For the reasons that were discussed during the interview and are summarized below, Applicants submit that, at the time of filing, Applicants had possession of the full scope of the claimed methods of identifying a therapeutic agent for treating Alzheimer's disease.

As discussed during the interview, the specification, rather than disclosing only *Appl*^{d}, discloses numerous Alzheimer's disease genes, defined as homologs of a human gene that has genetic variants associated with an increased risk of Alzheimer's disease or that encodes a gene product associated with Alzheimer's disease. While *Appl* and *Presenilin* (Psn) are exemplified as Alzheimer's disease genes useful in the invention, one skilled in the art also can practice the invention with one of a variety of other Alzheimer's disease genes. The specification further provides additional exemplary Alzheimer's disease genes, including genes disclosed in the specification itself as interacting (directly or indirectly) with *Appl*. Additional Alzheimer's disease genes that are disclosed in the specification, for example at page 14, as useful for practicing the methods of the invention include, for example, *Notch* (N), *Suppressor of Hairless* (Su(H)), *Delta* (Dl), *mastermind* (mam), *big brain* (bib), *halothane resistant* (har38), *cAMP-responsive element-binding protein A* (CrebA), *cAMP-responsive element-binding protein B* (CrebB, activator), *cAMP-responsive element-binding protein B* (CrebB, inhibitor), *α-adaptin*, *garnet* (δ-adaptin), and *shibire* (shi)(dynamin). Furthemore, the specification teaches that an Alzheimer's disease gene can be a gene that is differentially expressed at the mRNA or protein level in *Appl*^{d} flies as compared to *Appl*$^{+}$ flies and discloses several dozen specific examples of such Alzheimer's disease genes in Tables 4-6. One skilled in the art understand would have appreciated that Applicants were in possession of parental strains other than the Drosophila *Appl*^{D}, in sufficient numbers to show possession of the genus of parent strains that carry a mutation in an Alzheimer's disease gene.

In view of the above arguments and the interview on January 22, 2004, Applicants respectfully request removal of the rejection of claims 22 to 29 under 35 U.S.C. § 112, first paragraph, as lacking written description of the claimed invention sufficient to show that the inventors were in possession of the invention at the time the application was filed.

Enablement

Applicants traverse the objection to the specification and corresponding rejection of claims 22 to 29 under 35 U.S.C. § 112, first paragraph, as containing subject matter not described in the specification sufficiently to enable one skilled in the art to practice the invention.

Briefly, it is asserted that the specification lacks guidance with regard to the particular type of phenotype exhibited by the progeny and how such a phenotype may relate to Alzheimer's disease. The Examiner also asserts that the claims broadly read on transgenic organisms of any species while the specification does not provide commensurate guidance with regard to the preparation of creating transgenic organisms. In this regard, the Examiner cites several references to support the position that transgene expression is unpredictable. A further allegation of non-enablement focuses on the asserted lack of teachings directed to the selection of first parent strains other than *Appl*^{d} and second parent strains in general. Here, the Action points to a lack of guidance with regard to phenotypes that correlate with Alzheimer's disease and provides a further reference, which is alleged to set forth differences in expression of the Drosophila APPL protein and its mammalian homolog, APP.

The specification is alleged to fail in teaching types of phenotypes that may be observed in the progeny. Applicants submit that the specification teaches a variety of behavioral, morphological and other physical phenotypes useful in the methods of the invention including *Drosophila* phenotypes such as eye color, wing shape, bristle appearance, size, phototaxis and viability. Additional phenotypes useful for practicing the invention that are taught in the specification include the size, viability, eye color, coat color, or exploratory behavior of mice;

the size, viability, skin color, or optomotor response of zebrafish; the size, viability, phototaxis or chemotaxis of nematodes; and the colony color, colony size or growth requirements of yeast.

Further with regard to observable phenotypes, the specification teaches that viability is particularly useful for establishing a functional interaction between genes. Example I supports this teaching by demonstrating that flies carrying a combination of *Appl*^{d} and the chromosomal deficiency Df(1)N8, Df(1)JC19, 9Df(1)ct4bl, Df(1)lz-90b24 or Df(1)HF396 had significantly decreased viability as compared to sibling controls, while flies carrying *Appl*^{d} and the chromosomal deficiency Df(1)JF5, Df(1)2/19B or Df(1)RK2 had significantly increased viability as compared to sibling controls. With regard to a behavioral phenotype, Example III, shows that Appl^{d} Drosophila have a defect in fast phototaxis and the specification teaches that such a behavioral phenotype can be useful in the methods of the invention for establishing a functional interaction as is disclosed herein for Appl and Notch, Delta, α-adaptin, dCrebA and dCrebB. The specification further teaches, for example, at page 24, that altered phenotypes are represented by a significant change in the physical appearance or observable properties of the test progeny as compared to a sibling control and can be identified by sampling a population of test progeny and determining that the normal distribution of phenotypes is changed, on average, as compared to the normal distribution of phenotypes in a population of sibling controls. *See also* Example I.

With regard to the references provided by the Examiner directed to transgenic techniques, while not conceding non-enablement of transgenic methods, Applicants point out that enablement of every single embodiment within the scope of the claims is not a prerequisite for the enablement of the claimed methods. As taught in the specification, while the methods of the invention are exemplified using the genetic system Drosophila, any genetic system *suitable for transmission genetics and convenient analysis of test and sibling control progeny* is useful for practicing the methods of the invention (page 17, lines 1-10). In this regard, the specification further teaches that examples of genetic systems suitable for practicing the methods of the invention include, for example, mice (*Mus musculus*), zebrafish (*Danio rerio*), nematodes

(*Caenorhabditis elegans*), and yeast (*Saccharomyces cerevisiae* and *Schizosaccharomyces pombe*)(page 17, lines 1-10). Therefore, the specification explicitly teaches that the invention methods are contemplated to be practiced via transmission genetics such that the issue of enablement of transgenic methods is tangential to the enablement of the claimed methods. Applicants respectfully submit that the specification conveys to the skilled person that, at the time of filing, Applicants had possession of the claimed methods of identifying a therapeutic agent for treating Alzheimer's disease.

At the time of filing, those skilled in the art had knowledge that human disease gene homologs had been identified in a variety of genetic systems and, given the broad teachings and guidance for the use and applicability of the claimed methods with regard to species other than Drosophila, would have appreciated Applicants possession of the full scope of the claimed invention. In this regard the specification teaches, for example, at page 17, lines 14-29, homologs of human disease genes in a variety of other genetic systems including zebrafish, nematodes and yeast. Furthermore, for the various embodiments, the specification provides guidance with regard to practicing the invention in strains corresponding to a variety of genetic systems, for example, at page 39, lines 19-26, which discusses particular modes of administering an agent to mice, nematodes zebrafish and yeast. With regard to phenotypes useful for practicing the invention, the specification teaches that useful phenotypes include the size, viability, eye color, coat color, or exploratory behavior of mice; the size, viability, skin color, or optomotor response of zebrafish; the size, viability, phototaxis or chemotaxis of nematodes; and the colony color, colony size or growth requirements of yeast. These teachings would have conveyed to the skilled person, at the time of filing, that Applicants, while exemplifying the claimed methods using Drosophila, were in possession of the full scope of their claimed invention, which includes practice of the methods of identifying a therapeutic agent for treating Alzheimer's disease, in strains other than Drosophila and by utilizing transmission genetics.

Finally, with regard to the assertion at page 11 of Paper No. 17, that the Luo et al., *J. Neurosci.* 10(12):3849-3861 (1990) reference supports differences in the structure, regulation and function between the Drosophila APPL protein product and its mammalian homolog APP, Applicants respectfully disagree and point out that, according to the authors themselves, the reference provides evidence supporting the correlation between the Drosophila APPL protein product and its mammalian homolog APP. In this context the Examiner further cites Fossgreen *et al., Procl. Natl. Acad. Sci. USA* 95:13703-13708 (1998), for reporting that the expression of human APP in transgenic Drosophila results in a blistered wing phenotype that the Examiner argues appears unrelated to Alzheimer's disease.

As an initial observation, the presence of any altered phenotype in Drosophila can be related to Alzheimer's disease, given that the gene products are functionally equivalent and that flies are generally not subject to diagnosis with Alzheimer's disease or post-mortem autopsy to determine the presence of amyloid plaques. In this regard, the blistered wing phenotype, although not directly related to Alzheimer's disease, implicates the role of the gene product in cell-cell adhesion, which in turn is certainly related to Alzheimer's disease.

With regard to the Luo reference, the paper concludes its comparative study by indicating "[o]ur results provide further evidence that APP and APPL might be functionally homologous in their respective organsisms and suggest an ancestral nervous system function for this class of molecules." (Luo et al., page 3849, right hand column, third paragraph, last sentence). Therefore, according to the authors themselves, the reference provides evidence supporting the correlation between the Drosophila APPL protein product and its mammalian homolog APP. With regard to the Fossgreen *et a*l. reference, Applicants suggest that this reference establishes a γ-secretase activity in insects and acknowledges that this result supports the role of APP in cell adhesion and interaction with integrins, which Fossgreen further acknowledges to be associated with short tem memory in Drosophila and suggestive of a link with "memory mechanisms." (Fossgreen *et al.*, page 13707, right hand column, second

paragraph). Overall, both Luo et al. and Foss green et al. support a correlation in both structure and function between the Drosophila APPL protein product and its mammalian homolog APP.

In view of the above and the and the interview on January 22, 2004, Applicants request that the Office withdraw the objection to the specification and rejection of claims 22-26, 28 and 29 under35 U.S.C. §112, first paragraph, as allegedly lacking enablement.

Conclusion

In light of the Remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to contact the undersigned attorney with any questions related to this application.

Respectfully submitted,

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